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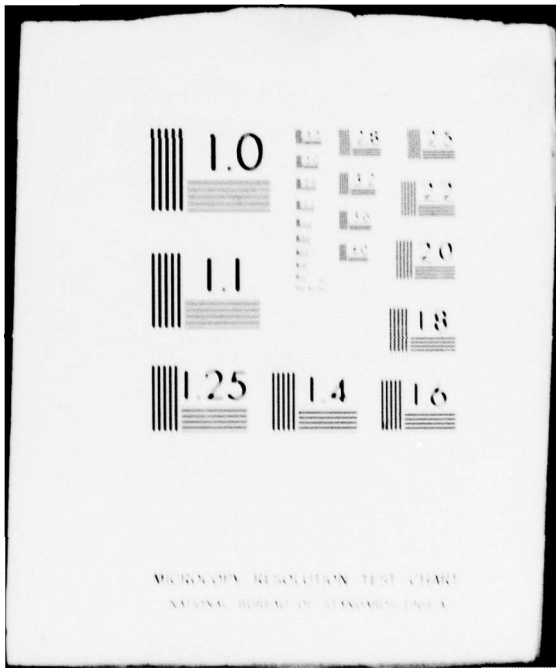
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PULMONARY ADAPTATION TO HIGH ALTITUDE

ANNUAL SUMMARY REPORT
(February 1, 1978 - December 31, 1978)

Jerome A. Dempsey, Ph.D.

December, 1978

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This project is aimed at two closely related questions concerning man's adaptation to high altitude hypoxia: (1) What mechanisms regulate the ionic composition of brain intra- and extra-cellular fluid in long-term hypoxia? and (2) What role do these regulatory factors play in mediating ventilatory acclimatization to hypoxia? In the second year of our contract, we have accomplished the following: (see continuation sheet)

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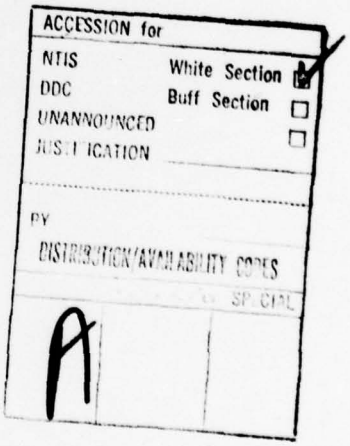
a) found that CSF [H+] changed as a function of ventilation during normoxia deacclimatization from chronic hypoxia;

b) established the rat as an animal model for human ventilatory acclimatization to chronic hypoxia, and observed the relative insensitivity of ventilation to alkaline brain perfusion in chronic hypoxia;

c) established the near-perfect regulation of brain pHi in short-term hypoxia and/or hypocapnia and determined the contribution of changes in brain metabolism to this regulation;

d) established the necessary biochemical and physiologic methods and then showed a close link between CNS serotonin metabolism and the control of air-breathing eupnea in the awake rat; and

e) showed the difference in and importance of ventilatory adaptation in other physiologic states--sleep and exercise.



ANNUAL PROGRESS REPORT
(Year 02 - February 1, 1978 - December 31, 1978)

This annual report summarizes the work we have completed during the second year of our research contract (February 1, 1978 to December 31, 1978) and therefore supplements our report for year 01. We are generally pleased with our progress over this second year of the contract, in that the specific objectives outlined at the initiation of years 01 and 02 have been accomplished. Year 01 was primarily a "methods development" phase and in year 02 we accomplished many of the proposed applications of these methods, determined which techniques and/or animal models were appropriate and which were not, and began new directions in techniques to provide better solutions to the proposed problems.

General and Specific Aims

The proposed studies have always been aimed at the major questions of: 1) what mechanisms regulate the intra- and extra-cellular environment of the brain in chronic hypoxia? and 2) what role do these regulatory processes play in explaining man's acclimatization to chronic hypoxia? Our major interest in "acclimatization processes has been one of ventilatory control mechanisms; although our studies have always also emphasized the physiological implications of this adaptive process--particularly in terms of pulmonary gas exchange and systemic oxygen transport in various physiologic states.

1. Role of brain extra-cellular fluid H+ in ventilatory acclimatization to chronic hypoxia.
2. Regulation of brain intra-cellular [H+] in chronic hypoxia.
3. Role of brain neurotransmitters in ventilatory control and acclimatization.
4. Implications of ventilatory adaptation to O_2 transport in various physiologic states.

PROGRESS TO DATE

I. Role of Brain ECF [H+] in Ventilatory Acclimatization.

Three studies were completed in Year 02 on this topic.

A. Anesthetized Dogs. Work dealing with the regulation of brain pHi in short-term hypoxia and hypocapnia (see Section II of this report) confirmed previous findings of ourselves and others that CSF pH moves in progressively alkaline directions over the initial 12 hours of moderate hypoxia and/or hypocapnia--a time during which these animals (when awake) show increasing ventilatory drives.

B. Awake Humans During "Deacclimatization"--i.e. over the first 24 hours in normoxia following 3-5 days acclimatization to hypoxia (4300 m) show a continued hyperventilation which slowly dissipates with time in normoxia. CSF (and plasma) pH in both species changed in a direction incompatible with ventilatory changes i.e. a) pH was normal (man) or significantly alkaline (pony) to sea-level control, while hyperventilation continued during the first hour return to normoxia; and b) as ventilation slowly declined toward

normal over 24 hours of normoxia, CSF pH became more and more acid. Thus both sets of findings speak strongly against a role for CSF pH in ventilatory acclimatization or deacclimatization from chronic hypoxia. These data were obtained in the middle and final portions of Year 01 and in Year 02 we analyzed the data, attempted various theoretical and experimental models to examine the question of how meaningful bulk CSF data relates to the real question of ventilatory control (see below), presented the data at FASEB national meetings and submitted a full manuscript to the Journal of Clinical Investigation (in October, 1978). We summarize these data in Figure 1 (attached). A very basic point this work brings up is the relative significance of brain ECF [H+] as a drive to breathe under circumstances of acute or chronic alterations in background stimuli or inhibitions to breathe--in hypoxia or normoxia.

C. Brain ECF Perfusion--The Question of How Meaningful Changes in CSF [H+] Reflect Those in the Brain Chemoreceptor [H+]. When we measure an alkaline CSF as breathing increases in hypoxia or an acid CSF as breathing decreases during deacclimatization in normoxia, we can conclude that ECF [H+] is playing no positive role as a causative factor in controlling breathing in these states. Based on the chronic steady-state nature of most of our data and that of others,we think our conclusion is correct. However, this crucial question must be addressed. One way has been to determine if a transependymal flux occurs between brain ECF and CSF via ventricular cisternal perfusion (as Fencl has done in goats, most recently in chronic hypoxia). Another approach is to determine if--as our bulk CSF [H+] changes indicate--the system actually changes "sensitivity" or gain to [H+] in acclimatization or deacclimatization. This has been our intended approach, i.e. to use ventricular-cisternal perfusion to determine the changing gain--if any--in the "central" chemoreceptors. To date, we have accomplished the following:

a) developed the study of ventilation, blood gases and metabolic rate in the awake rat and tested his pulmonary adaptation to high altitude (4300 m). We have analyzed, presented and published these data. In essence, the rat shows a unique human-like ventilatory acclimatization to hypoxia.

b) developed the technique of ventricular perfusion of mock CSF in the rat and with this technique fully described this animal's steady-state ventilatory response to varying acid-base perfusions in normoxia and on a few occasions in chronic hypoxia. Much of these normoxic control data have been analyzed and published. The long-term (6-8 hrs) perfusion in hypoxia have been very difficult to control and carry out although the few successful runs do confirm the conclusion from the correlative CSF data in man and pony--that the "central" chemoreceptor's response to Δ [H+] seems markedly reduced at least on a relative scale when other chronic stimuli are present--at least chronic hypoxia. Further development of better ventricular cannalae for perfusion has been recently completed and we hope this will lead to more successful studies in this model.

c) to supplement the rat studies we have begun to develop the goat as a model wherein ventricular-cisternal perfusion can be accomplished for the same purposes as stated above. To date we have trained 4 goats for study at rest and exercise and have chronically prepared carotid loops for arterial sampling. (USARIEM personnel have been invaluable in assisting us with the guide tube implants and we shall proceed with this surgery next).

These perfusion type studies--although preliminary to date--confirm our hypothesis that ventilatory acclimatization to and deacclimatization from chronic hypoxia is mediated by "extra-central chemoreceptor mechanisms." More generally, we propose that these kinds of data seriously question many very basic concepts concerning the relative importance of these chemoreceptors in ventilatory control in various physiologic states. A discussion of these concepts is included in four of our recently published reviews on the topic of ventilatory control. An example of some of our perfusion studies is shown in Fig. 2.

II. Regulation of Brain Intra-Cellular pH in Hypoxia and Respiratory Acid-Base Disturbances.

This question has been fairly thoroughly attacked by us this year. The following have been completed:

a) Technically--in dogs we established three methods for measuring brain intracellular pH (total CO_2, CPK equilibrium, and DMO-weak acid indicator) and brain ECF volume using ventricular-cisternal perfusion with labelled sulphate. These techniques for pHi were repeatedly modified until excellent agreement was finally achieved among them; the measurement of pHi in 4 different areas of brain was achieved and the results reported.

b) In vivo freezing techniques were established for brain tissue and fluorometric assays for brain metabolites were completed.

c) Pentobarbital and N_2O anesthesia were compared--the former showing marked effects on brain energy metabolism, and the results reported.

d) Most important, the effects of 5-12 hours of hypoxia (4300 m), or hypocapnia and their combination was tested. In all conditions, brain pHi in all 4 brain regions showed an initial alkalinity and then a return to normal values at a time when CSF remained alkaline to control levels (see example, Fig. 3). Changes in brain tissue metabolites accounted for some--but not all--of this excellent regulation of pHi. These data have been reported.

This time course of regulation of brain pHi correlates with that of ventilatory acclimatization--but does not prove a causal association. This possibility of a critical role for ΔpHi--either along with or in place of--ECF pH deserves careful exploration.

III. Brain Neurotransmitters and Ventilatory Adaptation.

This problem was investigated for two reasons: 1) a logical candidate in our search for an "extra-[H+]" mediator of ventilatory drive in the CNS; and 2) molecular O_2 is a substitute in the biosynthetic pathways of the brain monoamines--norephinephrine, dopamine and serotonin, and this synthesis is exquisitely sensitive to hypoxia.

This work began in Year 01 of the contract with technical methods and animal model development. In the second year we have accomplished the following:

a) provided a more efficient and accurate assay of brain neurotransmitter levels and have conducted initial studies on assays of systemic monoamines (in the gastrointestinal tract and carotid bodies of the rat).

b) completed our first extensive series of studies on the role of serotonin in the control of air-breathing eupnea. These data have been reported at FASEB and a manuscript has been submitted for publication. The key data aresummarized in Tables 1-3 and describe, in essence, our attempt to achieve more and more specificity in the pharmacologic blockade of CNS serotonin in the awake rat. We postulated from these data that some serotonin mediated nerve transmissions function under normal conditions to inhibit the inspiratory drive to breathe.

c) As a follow-up to these studies in eupnea we have initiated: (1) more extensive use of intra-ventricular injections of blocking agents to separate their central from peripheral i.e. carotid body, actions; (2) study of the effects of various forms of serotonin and nor-epinephrine blockade on the initial and time-course of response to hypoxia; and (3) analysis of dopamine in carotid body tissue and of the various monoamines in several brain regions rather than just whole brain.

We believe that these findings open up some new considerations concerning the role of CNS metabolism in the control of breathing. The implication of serotonergic mechanics relates closely to concepts of sleep and temperature regulation. It is likely that these serotonin mediated nerve transmissions are modulated by other sensory inputs. It is imperative, then, that these pharmacological, correlative-type studies be advanced further to discover the role of truly physiological changes in neurotransmitter metabolism on the control of ventilatory adaptations and to explore the interaction of these metabolic effects with the more classical "chemical" drives to breathe.

IV. Implications of Ventilatory Adaptations.

This problem was not specifically funded in Year 02 of the contract, i.e. it was replaced by a suggestion of the contract officer (see below, V). Nonetheless, we briefly report our progress to date in this area--because we feel they are of substantial practical significance to the whole question of pulmonary adaptation to hypoxia and will form an important phase of our proposed work for Year 03 of the contract.

We have begun to examine the importance of ventilatory adaptation in two physiologic states other than the resting, air-breathing state--namely, sleep and exercise. Our investigations of physiologic sleep have progressed in conjunction with Dr. James Skatrud (VA Hospital - Madison): a) an automated measurement circuit has been constructed and validated for continuous "non-invasive" measurements during sleep; b) we have examined the effects of chronic ventilatory stimulation (metabolic acidosis and progesterone) and inhibition (metabolic alkalosis and hyperoxia) on the sleep and ventilatory pattern and acid-base status during sleep (and exercise) in 2 normal subjects and one patient with chronic hypoxemia and CO_2 retention. It is our intention to expand this series of findings in normoxia and then to continue them during sleep in acute and chronic hypoxia for purposes of determining the nature of ventilatory adaptations to this potentially crucial physiologic state in hypoxia and to determine the effects of various pharmacologic interventions. Our initial findings will be presented at the 1979 FASEB national meeting.

Our exercise studies have concentrated on two types of non-steady-work to which the pulmonary system shows a less than the idealized response commonly portrayed for steady-state exercises. First, in prolonged moderate to heavy exercise, especially in hot environments in actual exercise in the field, we showed a progressive tachypneic hyperventilation coincident with arterial alkalosis and a variety of symptoms suggestive of respiratory muscle "fatigue" and dyspnea. Secondly, and most surprising, we have found a very high incidence of substantial arterial hypoxemia ($\% HbO_2 < 90\%$, $PaO_2 \sim 55$-70 mmHg) during the initial phases of short-term heavy work in normoxia. We believe this transient "failure" of pulmonary gas exchange in this type of exercise is closely linked with a lag of the hyperventilatory response behind an increasing pulmonary blood flow, and may be detrimental to systemic O_2 transport and thus physical performance. Theoretically this "failure" would be even more severe during exercise in chronic hypoxia. These findings have been reported in part and our work continues to describe the incidence of HbO_2 desaturation more thoroughly in healthy humans working in various types of non-steady-state work at sea-level.

V. Summary of Incompleted Work and Accomplishments in Year 02.

Two specific studies originally outlined in our application for Year 02 were not completed and/or discontinued. The effects of carbonic anhydrase inhibition on brain ECF composition (in rats) (as originally suggested by the USAMRDC Contracting Officer) was initiated but not followed up for several reasons--the major ones being initial negative results and the low success of our ventricular perfusion system in the rat for long-term perfusions. Our proposed ventricular perfusion and "cross perfusion" in the awake rat did not advance as far as originally perceived because of the unanticipated difficulties with perfusion methods. We are, however, pleased with the limited data we did obtain with this model, the new directions it did point us in and especially with the new methods and models we have initiated because of our progress with this technique.

On the positive side, we are very pleased with the completeness with which our goals were achieved concerning problems of brain intra-cellular pH regulation, brain metabolism in hypoxia, CSF [H+] studies in awake man and pony during deacclimatization from hypoxia, and with the relation of brain neurotransmitters to the control of breathing. Our advances in this latter problem are particularly

exciting because of the totally new concepts they offer to this confusing field of ventilatory control. Our purely correlative-type findings in the awake animal provide a sound basis for further detailed site of action-type neurophysiological investigation. Finally, we are also pleased with the progress in our application studies concerning the role of ventilatory adaptations in such practical physiologic states as sleep and muscular exercise. We feel these data are keys to a proper understanding of O_2 transport and its control in these states.

VI. Publications - Contract Year 02 (2/1/78 to 12/31/78)

A. Manuscripts Published or In Press

1. Dempsey, J.A., H.V. Forster, L.W. Chosy, P.G. Hanson and W.G. Reddan. "Regulation of CSF [HCO_3^-] during long-term hypoxic hypocapnia in man." J. Appl. Physiol. 44(2):175-182, 1978.

2. Olson, E.B., Jr. and J.A. Dempsey. "Rat as a model for humanlike ventilatory adaptation to chronic hypoxia." J. Appl. Physiol. 44(5):763-769, 1978.

*3. Dempsey, J.A. et al. "Is brain ECF [H+] an important drive to breathe in man?" Chest 73(2):251-253, 1978.

**4. Dempsey, J.A. "Role of the Brain in Exercise Hyperpnea." (In press). Proceedings of a Symposium on Exercise Hyperpnea - Science & Med. of Exercise & Sport.

*5. Forster, H.V. and J.A. Dempsey. "Chronic adaptation of ventilatory control mechanisms", (In press). In: Regulation of Breathing. Ed. T. Hornbein and C. Lenfant.

*6. Dempsey, J.A. et al. "Relative insensitivity of brain ECF [H+] as a ventilatory drive in awake humans." (In press). Proceedings of a Symposium on the Central Neural Control of Breathing. C. Von Euler, Editor (Stockholm, 1978).

B. Manuscripts Completed - Submitted for Publication Review (10/78 to 12/78)

1. Olson, E.B., Jr., D. McCrimmon, and J.A. Dempsey. "Role of CNS serotonin in the control of breathing in awake rats." Submitted to Science.

2. Musch, T., D. Pelligrino, and J. Dempsey. "Effects of pentobarbital vs. N_2O anesthesia on brain acid-base status and metabolism." Submitted to Brain Research.

3. Dempsey, J.A., H.V. Forster, et al. "Role of CSF [H+] in ventilatory deacclimatization from chronic hypoxia." Submitted to J. Clin. Invest.

**4. Hanson, P., J.A. Dempsey, and A. Claremont. "Hyperventilation during long-term exercise in the field." Submitted to J. Appl. Physiol.

B. Manuscripts Completed - continued

**5. Skatrud, J., and J.A. Dempsey. "Effects of MPA on ventilatory control in patients with chronic CO_2 retention and obstructive lung disease." Submitted to J. Clin. Invest.

C. Experimental Work Completed - Manuscripts in Preparation

1. Pelligrino, D., T. Musch, and J.A. Dempsey. "Control of brain pHi in hypoxia and/or hypocapnia."

*2. Dempsey, J.A., and H.V. Forster. "Ventilatory adaptations." (To be submitted to Physiol. Reviews by 9/1/79).

**3. Dempsey, J.A. et al. "Severe arterial hypoxemia during short-term heavy exercise on humans."

*4. Dempsey, J.A., E.H. Vidruk and S. Goodman. "Central nervous control of exercise hyperpnea." To Sport Sciences Review.

D. National and International Meetings - Abstracts & Presentations

1. 1978 - FASEB Meetings, Atlantic City, New Jersey. A total of 8 papers were presented by our laboratory, 5 of which were dependent in part or totally on the contract's funding. These published abstracts are not listed here, as they have since been submitted for publication in manuscript form.

2. 1979 - a) Work done under the Year 02 contract will be presented at the 1979 FASEB. Four abstracts will be submitted (by 1/2/79).

*,**b) Invited symposium presentations on ventilatory control and exercise physiology will be given at FASEB, April 1979 and on adaptation to chronic hypoxia will be given at the Banff Hypoxia Symposium, February 1979.

3. 1978 - Symposium on "Central Nervous Control of Breathing" in Stockholm, September 1978. Dr. J.A. Dempsey presented work on brain ECF [H+] and control of breathing.

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* Denotes invited review or "state-of-the-art" type invited presentations, summarizing our contributions drawn from experiments over many of the years the USAMRDC has supported the work of this laboratory.

** Denotes publications of our research on ventilatory adaptation in sleep and physical exercise which is not directly supported by our USAMRDC contracts, but represents important applications of our basic research (see body of progress report - Section IV).

VII. Military Significance.

A detailed discussion of this topic is contained in our original grant applications (and in our renewal application for 1979, Year 03). Briefly, our results in contract Year 02 have revealed the following, relevant to the well-being and performance of the soldier at high altitude:

- Basic Mechanisms. We have learned a great deal more about the brain's metabolism of neurotransmitters, the effect of hypoxia on same, their link with the vital process of ventilatory control and their modification by pharmacologic means. Further, we have detailed the human-like pulmonary response of rat to chronic hypoxia--thus establishing a unique and important experimental animal model. In man, pony and dog we have extended previous findings on the regulation of brain CSF H^+ during acclimatization to hypoxia to the phase of deacclimatization--from hypoxia--and showed the imperfect regulation of CSF pH in this critical "re-adjustment" phase. The near-perfect manner in which intra-cellular pH was regulated in these conditions points to the potential importance of functional implications of brain tissue metabolism in hypoxia.

- Applications to the soldier at high altitudes. Our work bears directly on this question in two major ways. First, we have been particularly careful to conduct our basic research with animals which realistically mimic human conditions. For example, the severity and duration of hypoxia and/or hypocapnia we routinely employ in our animal studies is based on our human observation at altitudes the soldier is likely to encounter (i.e. 3000-4500 m, hours to weeks of exposure, quick vs. gradual ascent, effects of sudden descent and then dissipation with time). Further, we are constantly aware of the necessity of choosing animal models which are as "human-like" as possible in their physiologic adaptations; and we have gone to considerable lengths to avoid the real problems of anesthesia and sedation in our experiments. Hence, we feel our work on brain metabolism and control of acid-base status is, for the most part, readily transferable to the human sojourner at high altitudes. Secondly, more immediate practical implications may be seen in our applied work with the physiologic states of sleep and exercise. It is the better understanding of physiologic adaptation and maladaptation to these states which is crucial to the sojourner at high altitudes. Further, it is imperative that we know ways of alleviating the physiologic problems and symptoms associated with these conditions to promote more optimum acclimatization, O_2 transport, and thus performance in the sojourner. We believe our initial studies are well along the way to achieving these practical goals.

VIII. Facilities.

Our research facilities are essentially the same as indicated in our original application, with the following additions or modifications:

a) Our on-campus hypobaric chamber facility was to have been ready by the summer of 1978, but has encountered numerous delays in construction. As

of 12/78 the chamber is now fully constructed and we expect to conduct research in this facility within the next 2 months.

b) We now have a sleep-physiology laboratory for human studies at the Madison VA Hospital. We have used some of our equipment and expertise in helping establish this facility and work cooperatively with the laboratory director, Dr. James Skatrud (Pulmonary Disease Chief - VA), on all sleep projects.

c) In the fall of 1978, we have added a neurophysiological approach to many of our studies. A neurophysiological laboratory has been established and is in the early stages of development.

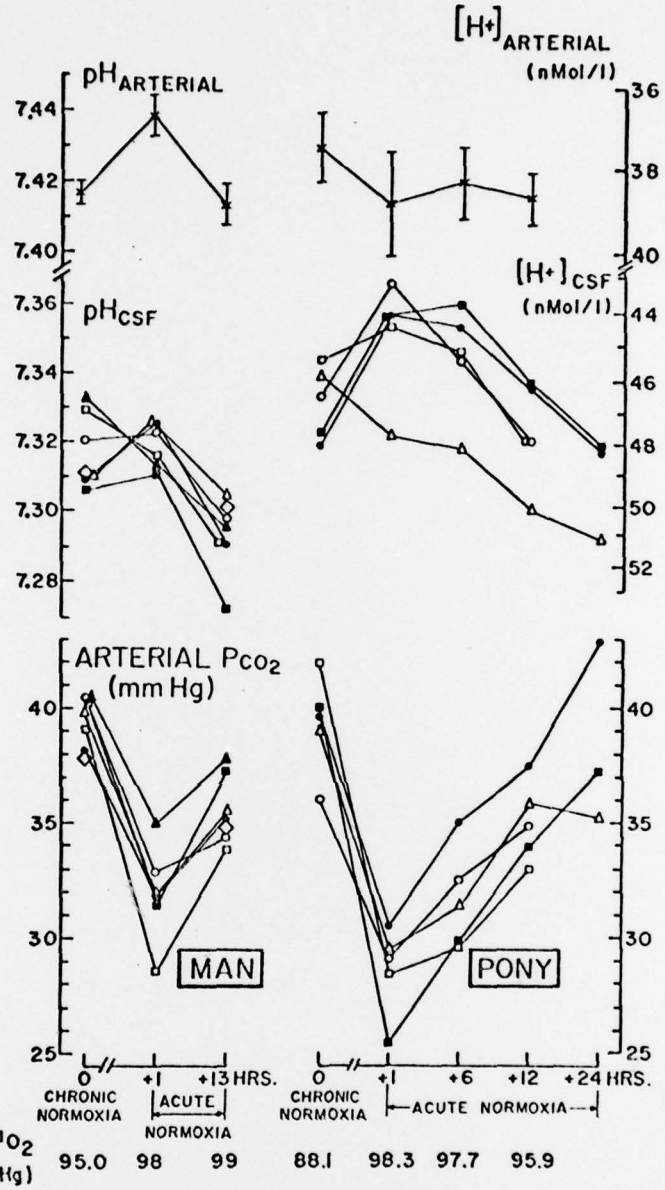

FIGURE 1. Individual subject changes in arterial blood pH and P_{O_2} and CSF pH in awake humans (lumbar CSF) and ponies (cisternal CSF) in normoxia, before and through 24 hours following 3-5 days sojourn to 4300 m.

Conditions: Chronic Normoxia - measurements taken at 250 m normoxia - control. Following these measurements 3 to 5 days of exposure to 4300 m hypoxia occurred (no measurements shown). Then the humans and animals were abruptly made normoxic and measurements of CSF and blood made over the ensuing 1-24 hours of Acute Normoxia.

The question was, "What role does CSF pH play in mediating the continued hyperventilation and its gradual dissipation in normoxia, following acclimatization to hypoxia?" Our data show no positive role for CSF pH. Note: a) at 1 hour of acute normoxia, hyperventilation persisted, but CSF pH is either no different (in humans) or significantly alkaline (in ponies) than that in chronic normoxia control; and b) between +1 and +13 hours acute normoxia, ventilation gradually fell and $PaCO_2$ rose; but CSF pH became more acid in all humans and all ponies. We conclude that CSF pH (and arterial pH) was a function of alveolar ventilation during deacclimatization from chronic hypoxia!!

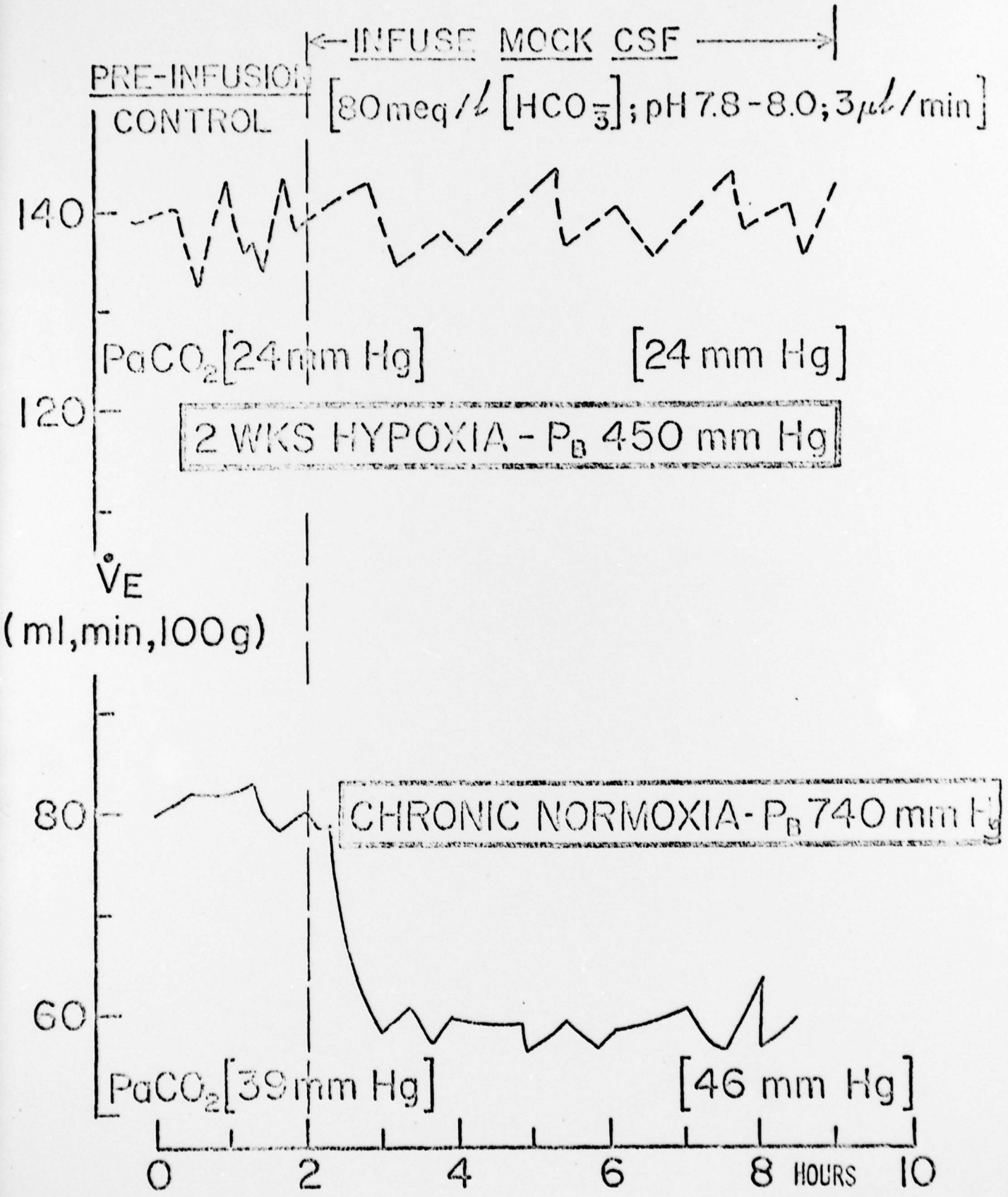

FIGURE 2. In the awake rat, ventilation was continuously measured and arterial blood sampled periodically in control and during 6 hours of perfusion via the lateral ventricle with a highly alkaline mock CSF. Note: in normoxia (at sea level), the expected hypoventilation is produced and

(continued on following sheet)

FIGURE 2. continued

maintained, but after 2 weeks of hypoxia the alkaline perfusion has no effect on ventilation. These are very preliminary data in 4 rats and they must be confirmed with better reproducibility. These data do, however, provide a rationale for intensive investigation of the possible change in gain of "central" chemoreceptors in various conditions where additional drives to breathe are present.

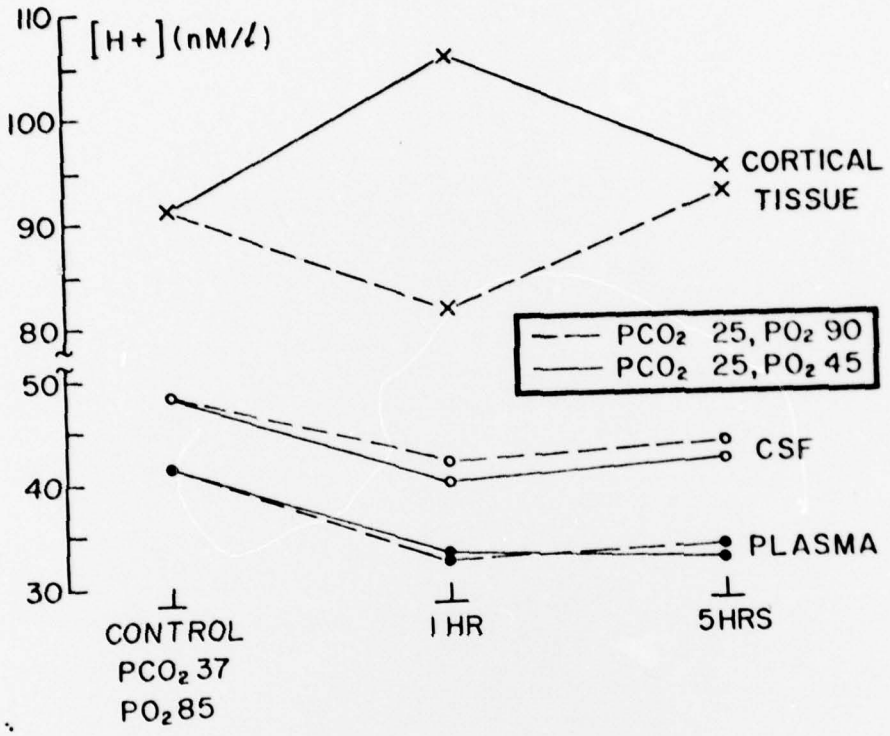

FIGURE 3. An example of regulation of brain extra- and intra-cellular pH in hypocapnia and hypoxic hypocapnia (mean data on 7 dogs in each of control, 1 and 5 hours of hypocapnia and hypoxic hypocapnia). Note: 1) CSF and plasma pH move in an alkaline direction at 1 hour and stay alkaline through 5 hours (and up to 12 hours in some additional experiments); 2) pHi is regulated back to control values by 5 hours; and 3) hypoxia alone contributed to changes in pHi at 1 but not 5 hours. This direction of change in cortical tissue pH was also found in 3 other areas of the brain, including the floor of the 4th ventricle.

TABLE. 1 Blocking agents used in the study of ventilatory control and CNS neurotransmitters.

DRUG	DOSE AND ROUTE OF ADMINISTRATION	TIME AFTER DOSE	MODE OF ACTION
RESERPINE	5 MG/KG Intramuscularly as Serpasil	2 days	Prevents storage of monoamine neurotransmitters
PCPA	300 MG/KG Intraperitoneally suspended in pH=2 1N HCl	2 Days	Inhibits Tryptophan Hydroxylase
AMT	300 MG/KG Intraperitoneally in pH 10 - 11 saline	5 HR Average (1 - 13 HR)	Inhibits Tyrosine Hydroxylase
6-FT	100 MG/KG Intraperitoneally in pH 9 - 10 saline	4 HR	Inhibits Tryptophan Hydroxylase
PCA	5 MG/KG Intraperitoneally in saline	2 Days	Releases Serotonin (5-Hydroxytryptamine), Inhibits Tryptophan Hydroxylase, Serotonergic neurotoxicity
5,7-DHT	80 - 200 UG in 20 Ul saline + 0.1% ascorbate Intracerebroventricularly 1 HR after Desipramine 25 MG/KG Intraperitoneally in saline	10 - 18 Days	Cytotoxic for nerve cells containing Serotonin

TABLE 2. Control values (mean ± 95% confidence limits, N) in the awake rat for ventilation, metabolic rate, blood gases and brain monoamine concentrations.

	$\bar{x} \pm$ 95% CL	
Body Weight, g	334 ± 6	(306)
Rectal Temp., °C	38.0 ± 0.1	(277)
PaO_2, Torr	85 ± 1	(236)
$PaCO_2$, Torr	39.9 ± 0.3	(236)
$[HCO_3^-]_a$, mEq/L	26.3 ± 0.2	(235)
pHa	7.435 ± 0.002	(235)
Hematocrit, %	42.9 ± 0.5	(162)
$\dot{f}$, breaths/min	114 ± 3	(249)
V_T/ ml	2.11 ± 0.04	(249)
$\dot{V}_E$, $ml \cdot min^{-1} \cdot 100g^{-1}$	72 ± 1	(249)
$\dot{V}_{O_2}$, $ml \cdot min^{-1} \cdot 100g^{-1}$	2.5 ± 0.1	(192)
$\dot{V}_E/\dot{V}_{O_2}$	30.2 ± 0.8	(183)
NE, ng/g	791 ± 37	(083)
DA, ng/g	891 ± 54	(083)
5HT, ng/g	627 ± 31	(083)

TABLE 3. Effects of pharmacologic blockade on ventilation and brain NE, DA and 5HT concentrations.

	$\Delta PaCO_2$ (mmHg)	ΔpHa	$\Delta[HCO_3^-]_a$	$\Delta\dot{V}_E/\dot{V}_{O_2}$	ΔNE (%)	ΔDA (%)	$\Delta 5HT$ (%)
RESERPINE	-8.8 ± 3.4 (6) **	.04 ± .02 (6) **	-2.4 ± 2.1 (6) *	0.2 ± 10.7 (6)	-91 ± 8 (3) **	-91 ± 32 (3) **	-86 ± 20 (3) **
PCPA	-7.2 ± 0.8 (30) **	.04 ± .01 (29) **	-2.5 ± 0.6 (29) **	5.0 ± 3.0 (12) *	-22 ± 11 (12) *	4 ± 16 (8)	-76 ± 15 (8) **
AMT	-0.3 ± 2.1 (5)	.02 ± .03 (5)	1.0 ± 1.7 (5)	4.4 ± 5.9 (6)	-86 ± 5 (15) **	-73 ± 6 (15) **	+63 ± 14 (15) **
6-FT	-5.9 ± 1.4 (11) **	.06 ± .01 (11) **	-0.3 ± 0.9 (11)	4.0 ± 3.6 (10) *	- 2 ± 6 (5)	- 4 ± 9 (5)	-40 ± 10 (5) **
PCA	-5.4 ± 1.1 (8) **	.02 ± .03 (8)	-2.6 ± 1.2 (8) **	4.3 ± 4.2 (8) *	- 4 ± 13 (5)	- 1 ± 5 (5)	-51 ± 14 (5) **
5,7-DHT	2.1 ± 1.5 (10) *	.01 ± .01 (10)	1.7 ± 1.0 (10) *	-0.9 ± 2.7 (10)	9 ± 8 (20) *	-16 ± 13 (20) *	-60 ± 11 (20) **

Mean ± 95% confidence limits (number treated)

Difference significant * $P < .05$
** $P < .01$

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